

**REMARKS**

The Office Action of August 20, 2001 presents the examination of claims 1-8. Claims 7 and 8 are canceled. Claims 1, 3-4, and 6 are amended. No new matter is inserted into the application.

***Rejection under 35 U.S.C. § 102(b)***

The Examiner rejects claims 7 and 8 under 35 U.S.C. § 102(b) for allegedly being anticipated by Applicants' admissions in the specification. ~~Claims 7 and 8 are canceled, thus rendering~~ rejection of said claims moot.

***Rejection under 35 U.S.C. § 103(a)***

The Examiner rejects claims 1-6 under 35 U.S.C. § 103(a), for allegedly being obvious over the combination of Lindberg et al. (Pharmacology & Toxicology) in view of Clerico et al. (Clinical Chemistry). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

***The Present Invention***

The present invention is directed to a method for measuring mammalian natriuretic peptide using containers made of, or coated with, a material that does not covert an inactive form of

substances that degrade mammalian natriuretic peptide into an active form. This material may be, for example, silicone or plastic.

Distinctions between the present invention and the cited references

Lindberg et al. discloses the adsorption of atrial natriuretic peptide (ANP) to various materials, such as siliconized glass and polypropylene. Lindberg et al. indicates that the degradation of ANP results from adsorption on the silicone coated container.

Lindberg et al. fails to disclose a method for inhibiting the activation of substance degrading natriuretic peptides using specialized containers.

Clerico et al. discloses the degradation of ANP, a mammalian natriuretic peptide. Clerico et al. discloses that inhibiting agents, approtinin, and EDTA indirectly inhibit ANP by the direct inhibition of the activity of substances degrading the mammalian natriuretic peptides. Clerico et al. fails to disclose or suggest a method for inhibiting the activation of substance degrading natriuretic peptides using specialized containers.

The Examiner asserts that it would obvious to combine the disclosures of prior art references, specifically the containers of Lindberg and the storage methods of Clerico, because "it would appear from Lindberg that silicone coated-containers do not degrade

ANP... ." Applicants respectfully disagree and submit that the Examiner is using improper hindsight reconstruction to combine the disclosures of Lindberg et al. and Clerico et al. The Examiner is reminded that the motivation must be formed in the prior art references or in the common knowledge at the time. Here, however, there is no motivation to combine the two references, because neither reference discloses that specialized containers prevent the degradation of natriuretic peptides. As such, the instant rejection is improper and should be withdrawn.

***Rejection under 35 U.S.C. § 112, second paragraph***

The Examiner rejects claims 1-8 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Claims 7 and 8 are canceled, thus rendering the rejection applied to said claims moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

These rejections are basically for grammatical and idiomatic errors. In response to the Examiner's remarks, Applicants amend have the claims to recite proper idiomatic English.

Applicants respectfully submit that the above amendments render the instant claims in full compliance with 35 U.S.C. § 112,

second paragraph. Thus, Applicants respectfully request that the instant rejection applied to said claims is withdrawn.

***Issues under 35 U.S.C. § 112, First Paragraph***

**Written Description**

The Examiner rejects claims 5 and 8 under 35 U.S.C. § 112, first paragraph for allegedly not being described in the specification. Claim 8 is canceled, thus rendering the rejection applied to said claim moot. ~~Applicants respectfully traverse the~~ rejection applied to the pending claim. Reconsideration and withdrawal of the instant rejection are respectively requested.

Specifically, the Examiner asserts that the term "aprotinin" is not found in the specification. Applicants respectfully disagree. Disclosure of "aprotinin" is found on page 4, lines 18-19 of the specification, wherein it is recited that the invention "relates to a measurement of natriuretic peptide in specimens which do not contain aprotinin."

Thusly, Applicants respectfully submit that the instant rejection is improper and should be withdrawn.

**Enablement**

The Examiner further rejects claims 2-5 for allegedly not being enabled by the specification. Applicants respectfully

traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the specification does not provide enablement for "silicone or plastic." Specifically, on page 5, first paragraph of the Office Action, the Examiner writes, "the terms 'silicone or plastic' lack enablement as it would require one of ordinary skill in this art undue experimentation to determine which such substance would work in the instant invention."

~~Applicants respectfully disagree. The Examiner is reminded that~~  
the specification need not include, and preferably omits, what is well known in the art. Spectra-Physics Inc. v. Coherent Inc., 827 F.2d 1524 (CAFC 1987).

As evidence that the properties of the different types of silicone and plastics are known in the art, Applicants submit copies of three catalogues (Nunc Catalogue 2001/2002, Nalgene Labware 2000, and Sigma 1999) as Exhibits 1-3, respectively. These catalogues are widely available. The present inventors have used the basic different types of plastics, such as polystyrene, polypropylene, polyethylene, polyethylene terephthalate, acrylic resin, and silicone, as all disclosed in the specification, in preparing the instant containers. The basic skeleton of such plastics is disclosed in the catalogues. Silicone polymer comprises a structural unit represented by the formula  $[R_nSiO(4-$

$n/2)m$ , where  $n=1-3$  and  $m>1$ . R groups are usually methyl, longer alkyl, fluoroalkyl, phenyl, vinyl, alkoxy, or alkylamino. Thus, one of ordinary skill in this art can predict that other types of plastics and silicone comprising the same or similar skeleton have the same or similar properties. Accordingly, the types of plastics that would work in the present invention are not unpredictable.

For all of the above reasons, Applicants respectfully submit that all of the instant claims comply with 35 U.S.C. § 112, first paragraph, and respectfully request that the instant rejection be withdrawn.

#### **Title**

The Examiner states a new, more descriptive title is required. In response to the Examiner's remarks, Applicants amend the title accordingly. Thus, the instant objection is overcome.

#### **Abstract**

The Examiner objects to the abstract for grammatical and idiomatic errors. In response to the Examiner's remarks, Applicants submit a modified abstract herewith. Thus, the instant objection is overcome.

***Disclosure***

The Examiner objects to the disclosure for various grammatical and idiomatic errors. The disclosure is amended herein in accordance with the Examiner's remarks. Therefore, the instant objection is overcome.

***Summary***

Overall, the present invention possesses significant patentable features that the cited prior art references do not possess. Furthermore, Applicants submit that the claims are fully in compliance with 35 U.S.C. § 112, first and second paragraphs. All of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action on the merits of the present application is thereby requested.

If there are any minor matters precluding allowance of the present application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at (703) 205-8000.

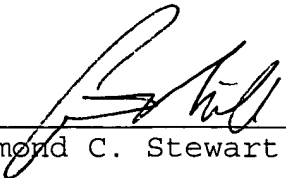
If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

Appl. No. 09/530,013

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17;  
particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By  #32,868  
for Raymond C. Stewart, #21,066

RCS/<sup>KLR</sup>KLR  
0032-0254P

P.O. Box 747  
Falls Church, VA 22040-0747  
(703) 205-8000

Attachment: Version with Markings to Show Changes Made  
Exhibits 1-3  
Abstract





RECEIVED

NOV 23 2001

TECH CENTER 1600/2900 Appl. No. 09/530,013

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Title:

The title has been amended as follows:

[METHOD FOR INHIBITING DEGRADATION OF NATRIURETIC PEPTIDES AND  
IMPROVED METHOD FOR MEASURING NATRIURETIC PEPTIDES WITH THE USE OF  
THE SAME]

--METHOD FOR INHIBITING DEGRADATION OF NATRIURETIC PEPTIDES THROUGH  
USE OF SPECIALIZED CONTAINERS UPON MEASURING AND HANDLING OF  
SPECIMEN--.

In the Specification

The paragraph beginning on page 2, line 10, has been amended  
as follows:

It is speculated that after blood collection natriuretic  
peptides are degraded by substances such as proteases in blood. To  
date, some protease inhibitors were added into the samples for the  
inhibition of the degradation of natriuretic peptides. But, it  
could not completely inhibit the degradation. The present  
inventors have speculated that coagulation factors activated by  
negatively charged solid phase such as glass surface accelerate the  
degradation of natriuretic peptides when specimens are collected  
into a container made of glass. The inventors have collected  
specimens by using a glass container wherein the face coming into

contact with a specimen [specimens] was coated with silicone [silicon], and obtained a result that the degradation of natriuretic peptides were inhibited.

The paragraph beginning on page 7, line 11, has been amended as follows:

(1) Preparation of [silicon] silicone-coated PET tubes: Commercially available PET tubes (Terumo, Tokyo, Japan) were washed with purified water once, and with 3% (V/V) silicone solution (SILICONIZE L-25: Ficon Co.) three times. They were washed once again with purified water and dried.

The paragraph beginning on page 8, line 12, has been amended as follows:

As specimen storing containers, glass tubes, silicone [silicon] coated glass tubes, and plastic tubes were used. Five kinds of plastic tubes, i.e., polystyrene tubes, polypropylene A tubes, polypropylene B tubes, reinforced polyethylene tubes, and acrylic resin tubes were used.

The paragraph beginning on page 9, line 6, has been amended as follows:

The residual activity of BNP remarkably decreased in glass tubes because BNP was degraded by substances degrading the peptides such as proteases. Conversely, [While] the decrease of the residual BNP activity was suppressed in [silicon] silicone-coated glass tubes. Furthermore, in plastic tubes made of polyethylene terephthalate, polystyrene, polypropylene, polyethylene or acrylic resin coated with or without silicone, the degradation of BNP was suppressed due to the inhibition of the activation of substances degrading peptides.

**IN THE ABSTRACT:**

The Abstract has been amended as follows:

A method for inhibiting the degradation of mammalian natriuretic peptides, in particular[,] BNP, by using containers wherein the face coming into contact with specimens are made of a material is disclosed [capable of inhibiting the activation of a substance degrading peptides]. Said material inhibits the activation of a substance, which in turn, degrades the peptides. This method makes it possible to collect specimens for measuring natriuretic peptides stably and conveniently. Also provided is a method for measuring natriuretic [natriureitc] peptides by using these containers.

In the Claims:

The claims have been amended as follows:

1. (Twice Amended) A method for inhibiting the degradation of mammalian natriuretic peptides in a specimen, comprising: [which comprises]

placing [using, upon handling] the specimen[,] into a container, wherein the face coming into contact with the specimen is made of or coated with a material,

wherein said material inhibits ~~[inhibiting]~~ ~~the activation of~~  
a substance, which substance if not activated, cannot degrade  
[degrading] the mammalian natriuretic peptides.

3. (Amended) The method as claimed in claim 1 or 2, wherein said [mammal] specimen is obtained from a human, dog, pig, rat  
[and] or mouse.

4. (Twice Amended) The method as claimed in claim 1 or 2, wherein said natriuretic peptide is brain natriuretic peptide (BNP)  
[BNP].

6. (Amended) A method for measuring mammalian natriuretic peptides in a specimen, [which comprises] comprising the steps of:

employing a container, upon handling the specimen, comprising a material, wherein said material inhibits the activation of a substance, which substance if not activated, cannot degrade the mammalian natriuretic peptides; and

measuring the mammalian natriuretic peptides by standard means  
[the method as claimed in claim 1].